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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
GODDARD, LAURA B	

ART UNIT	PAPER NUMBER
1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/580,131	FRANCIS-LANG ET AL.	
	Examiner	Art Unit	
	LAURA B. GODDARD	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 April 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-25* is/are pending in the application.

4a) Of the above claim(s) *4,5,7,11-15 and 18-25* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,6,8-10,16 and 17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/5/07, 7/18/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The response filed on April 12, 2010 to the restriction requirement of November 10, 2009 has been received. Applicant has elected with traverse Group I, claims 1-12 and 16-19, and the species of "PLK nucleic acid," "cell proliferation assay," method further comprising steps (d)-(f)," "cell culture assay system" for the first and second assays, for examination. Because Applicant did not distinctly and specifically point out any errors in the restriction requirement, the election has been treated as an election without traverse (MPEP 818.03(a)). Claims 1-25 are pending. Claims 13-15 and 20-25 have been withdrawn from further consideration by the examiner under 35 CFR 1.142(b) as being drawn to non-elected inventions. Claims 4, 5, 7, 11, 12, 18, and 19 are withdrawn as being drawn to non-elected species. Claims 1-3, 6, 8-10, 16, and 17 are currently under prosecution as drawn to the elected species.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1-3, 6, 8-10, 16, and 17 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The claims are drawn to a method of identifying a candidate beta catenin pathway modulating agent, said method comprising the steps of: (a) providing an assay system comprising a PLK polypeptide or nucleic acid; (b) contacting the assay system with a test agent under conditions whereby, but for the presence of the test agent, the system provides a reference activity; and (c) detecting a test agent-biased activity of the assay system, wherein a difference between the test agent-biased activity and the

reference activity identifies the test agent as a candidate beta catenin pathway modulating agent.

The specification discloses the discovery of genes that modify the beta catenin pathway in and Drosophila, and identified their human orthologs, hereinafter referred to as Polo Like Kinase (PLK). The invention provides methods for utilizing these beta catenin modifier genes and polypeptides to identify PLK-modulating agents that are candidate therapeutic agents that can be used in the treatment of disorders associated with defective or impaired beta catenin function and/or PLK function. Preferred PLK-modulating agents specifically bind to PLK polypeptides and restore beta catenin function. Other preferred PLK-modulating agents are nucleic acid modulators such as antisense oligomers and RNAi that repress PLK gene expression or product activity by, for example, binding to and inhibiting the respective nucleic acid (i.e. DNA or mRNA). The specification discloses that sequences related to PLK nucleic acids and polypeptides that can be used in the invention are disclosed in Genbank (referenced by Genbank identifier (GI) number) as GI#s 21361432 (SEQ ID NO: 1), 7657626 (SEQ ID NO:2), 14721506 (SEQ ID NO:3), 16215695 (SEQ ID NO:4), and 23243308 (SEQ ID NO:5) for nucleic acid, and GI#21361432 (SEQ ID NO:6) for polypeptide sequences ([0014]). Examiner notes that according to Genbank, these nucleic acid identifier numbers refer to PLK4 (also known as "SAK" or "STK18").

In the Examples, section I, the specification discloses that two dominant loss of function screens were carried out in Drosophila to identify genes that interact with the Wg cell signaling molecule, beta-catenin. Late stage activation of the pathway in the

developing Drosophila eye leads to apoptosis, whereas early stage activation leads to an overgrowth phenotype. Modifiers of the phenotypes were identified as either members of the Wg pathway, components of apoptotic related pathways, components of cell cycle related pathways, or cell adhesion related proteins. Drosophila POLO was identified as a suppressor from the screen. Orthologs of the modifiers are referred to herein as PLK ([0113-0123]).

The specification discloses in section VII RNAi experiments to knock down expression of PLK (SEQ ID NO:1, PLK4) in various cell lines using small interfering RNAs. The results of these experiments indicated that RNAi of PLK decreases proliferation in LOVO and HT29 colon cancer cells and PC3 prostate cancer cells. Standard colony growth assays were employed to study the effects of decreased PLK expression on cell growth. Results indicated that RNAi of PLK decreased proliferation in HT29 and SW480 colon cancer cells ([0145]).

In relevant art, there are actually five PLK's in humans alone, and polo-like kinases are found in several unrelated species (see iHOP "information hyperlinked over proteins", p. 1-3). Eckerdt et al (Oncogene, 2005, 24:267-276) teach that although PLK's share two conserved elements, the N-terminal Ser/Thr kinase domain and a highly homologous C-terminal region termed polo-box motif, their functions diverge considerably. While PLK1 is inhibited by different cell division check point pathways, PLK2 and PLK4 are activated by the spindle checkpoint or the DNA damage checkpoint (abstract; p. 268, col. 1; Figure 1). Enhanced PLK1 activity accelerates cellular proliferation at least in the M phase and PLK1 is known to be overexpressed in several

cancers (p. 269, col. 2 to p. 270, col. 1). PLK3 appears to be a tumor suppressor and is reduced in expression for tumors (p. 270, col. 1-2). Controversial data exists for the expression profile of PLK4. While one study observed PLK4 expression restricted to testis and thymus, another study found that expression of PLK4, like PLK1, is associated with mitotic and meiotic cell division, and PLK4 is overexpressed in colorectal tumors. Eckerdt et al teach that further studies are required to elucidate the role of PLK4 in oncogenesis in more detail (p. 270, col. 2).

Habedanck et al (Nature Cell Biology, 2005, 7:1140-1146) teach that PLK4 is the most structurally divergent Polo family member and is a regulator of centriole duplication (abstract). Habedanck et al teach that the physiological substrates of PLK4 remain to be identified (p. 1145, col. 1). Pellegrino et al (Hepatology, 2010, 51:857-868) teach that levels of PLK1 were progressively increased from non-neoplastic surrounding liver tissues to hepatocellular carcinoma (HCC), reaching the highest expression in tumors with poorer outcome. In sharp contrast, PLK2, PLK3, and PLK4 mRNA and protein expression gradually declined form nontumorous liver to HCC, with the lowest levels being detected in HCC with shorter survival time. In liver tumors, PLK2-4 down regulation was paralleled by promoter hypermethylation and/or loss of heterozygosity at the PLK2-4 loci. PLK1 inhibition led to suppression of cell growth, while the opposite effects followed PLK2-4 silencing in HCC cell lines. Pellegrino et al conclude that PLK1-4 proteins are aberrantly regulated and possess different roles in human HCC, with PLK1 acting as an oncogene and PLK2-4 being presumable tumor suppressor genes (abstract).

One cannot extrapolate the disclosure of the specification to the enablement of the claims because the specification does not provide guidance or examples for predictably identifying a beta-catenin pathway modulating agent comprising contacting a PLK nucleic acid or cell expressing the nucleic acid with a test agent and detecting a test agent-biased activity. The specification discloses only the identification of *Drosophila* POLO protein as altering a phenotype in fruit flies that identifies it as being any of: members of the Wg pathway, components of apoptotic related pathways, components of cell cycle related pathways, or cell adhesion related proteins. Subsequently, the specification identifies PLK4 as a human ortholog of *Drosophila* POLO and demonstrates that RNAi of PLK4 (SEQ ID NO:1) decreased proliferation in HT29 and SW480 colon cancer cells. The specification fails to provide a nexus between PLK4 or any PLK and the beta-catenin pathway, therefore one of skill in the art could not predictably identify a beta-catenin pathway modulating agent using the claimed methods.

Further, the art (above) demonstrate that the PLKs have very different functional roles and PLK4 (the only exemplified and structurally disclosed PLK in the specification) is the most structurally divergent Polo family member. According to the state of the art (above), it appears that very little is known about PLK4, its substrates are unknown, and its role in cell proliferation is highly variable. In contrast to the specification, Eckerdt et al teach controversial data exists for the expression profile of PLK4 and Habedanck et al teach PLK1 inhibition led to suppression of cell growth, while the opposite effects followed PLK2-4 silencing in HCC cell lines. The claims are broadly drawn to assay

systems comprising *any* PLK nucleic acid, and it is clear from the art that each PLK is structurally and functionally distinct and play different roles in cell division or cell growth, therefore the measured test-agent biased activity of the claimed assay using one PLK would not reasonably extrapolate to the measured results of using a different PLK. Given the specification exemplifies only a single PLK, PLK4, given the specification fails to provide any nexus between the beta-catenin pathway and any PLK, given the art teaches each PLK1-4 are structurally and functionally distinct including their effects on cell proliferation, and the substrates of PLK4 are unknown, a high quantity of experimentation would be required to determine which PLK nucleic acid in what assay system, and what test agent-biased activity would be required to predictably identify a beta-catenin pathway modulating agent.

It is noted that MPEP 2164.03 teaches that "the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability of the art. In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The amount of guidance or direction refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as how to make and use the invention in order to be enabling." A review of the prior art reveals no nexus taught between any PLK and

beta-catenin or its pathway. Given the unknown substrates of PLK4, the structural and functional divergence of the PLKs, the lack of adequate disclosure in the specification, and that little is known in the art about the claimed invention, one of skill in the art would be forced into undue experimentation to practice the claimed invention.

Finally, the most relevant post-filing art is taught by Arai et al (Cell Cycle, 2008, 7:3556-3563). Arai et al, published five years after the priority date of the instant claims, teach that beta-catenin is identified as a novel substrate of PLK1. Arai et al teach that PLK1 has numerous substrates (p. 3556, col. 2; p. 3560, col. 1), therefore an assay system as claimed comprising PLK1 could produce a test agent-biased activity that could result from PLK acting or failing to act on *any* of its numerous substrates unrelated to beta-catenin, and one of skill in the art could not predict that the test agent-biased activity was a result related to the beta-catenin pathway and could not predict the agent modulates the beta-catenin pathway. Arai et al demonstrate that FLAG-PLK1 overexpressed in human embryonic kidney cells coimmunoprecipitated with beta-catenin (p. 3557, col. 2) and GST-beta-catenin was does-dependently phosphorylated by PLK1 (p. 3557, col. 2). The phosphorylation of beta-catenin was suppressed by knock-down of endogenous PLK1 with siRNA in cells (p. 3559, col. 1). After further experimentation, Arai et al provide a direct nexus between PLK1 and beta-catenin. In contrast, the specification discloses nothing about PLK1 and fails to provide a nexus between any PLK and the beta-catenin pathway. The specification discloses only PLK4, which is now known to be the most structurally divergent polo-like kinase and is demonstrated to function as a tumor-suppressor, the opposite of PLK1.

Therefore, in view of the state of the art, what little is known in the art, the quantity of experimentation necessary, the breadth of the claims, lack of guidance in the specification, and the absence of working examples, it would require undue experimentation for one skilled in the art to practice the invention as claimed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

3. Claims 1, 2, 6, 8, 9, 16, and 17 are rejected under 35 U.S.C. 102(b) as being anticipated by Spankuch-Schmitt et al (Oncogene, 2002, 21:3162-3171).

Spankuch-Schmitt et al teach a method comprising: (a) providing a cell culture assay system expressing PLK1 nucleic acid; (b) contacting the cell culture assay system with a PLK1 antisense oligomer test agent or control agent; and (c) detecting cell proliferation effects of the test agent or control agent, wherein PLK1 antisense inhibited cell proliferation and PLK1 protein production compared to the control (Figure 1; Figure 3; p. 3167, col. 1-2). Spankuch-Schmitt et al teach conducting this assay in three cell culture systems: MDA-MB-435 breast cancer cells, A549 lung cancer cells, and HeLa S3 cervical cancer cells (p. 3163, col. 1; Figure 3), hence Spankuch-Schmitt

et al teach conducting the additional steps of providing a secondary assay system in a different cell culture as instantly claimed.

4. **Conclusion:** No claim is allowed.

5. Any inquiry concerning this communication or earlier communications from the examiner should be directed to LAURA B. GODDARD whose telephone number is (571)272-8788. The examiner can normally be reached on 7:00am-3:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Laura B Goddard/
Primary Examiner, Art Unit 1642